

We claim:

1. A liposome comprising at least one phosphatidylcholine, a cholesterol, and a benzoquinazoline thymidylate synthase inhibitor.

2. The liposome of claim 1 wherein said phosphatidylcholine is selected from the group consisting of distearoylphosphatidylcholine, hydrogenated soy phosphatidylcholine, soy phosphatidylcholine, egg phosphatidylcholine, hydrogenated egg phosphatidylcholine, dipalmitoylphosphatidylcholine, dioleoylphosphatidylcholine, dielaidoylphosphatidylcholine, and dimyristoylphosphatidylcholine.

3. The liposome of claim 2 wherein said phosphatidylcholine is hydrogenated soy phosphatidylcholine.

4. The liposome of claim 2 wherein said phosphatidylcholine is soy phosphatidylcholine.

5. The liposome of claim 2 wherein said phosphatidylcholine is dioleoylphosphatidylcholine.

6. The liposome of claim 2 wherein said phosphatidylcholine is dielaidoylphosphatidylcholine.

7. The liposome of claim 2 wherein said liposome further comprises phosphatidylglycerol.

8. The liposome of claim 3 wherein said benzoquinazoline thymidylate synthase inhibitor is GW1843.

9. The liposome of claim 4 wherein said benzoquinazoline thymidylate synthase inhibitor is GW1843.

10. The liposome of claim 5 wherein said benzoquinazoline thymidylate synthase inhibitor is GW1843.

11. The liposome of claim 6 wherein said benzoquinazoline thymidylate synthase inhibitor is GW1843.

5 12. The liposome of claim 7 wherein said benzoquinazoline thymidylate synthase inhibitor is GW1843.

13. The liposome of claim 12 wherein said hydrogenated soy phosphatidylcholine, cholesterol and phosphatidylglycerol are in a molar ratio of about 2:1:0.1.

10 14. The liposome of claim 8 wherein the hydrogenated soy phosphatidylcholine to cholesterol molar ratio is from about 5:1 to 2:1.5.

15. The liposome of claim 14 wherein said molar ratio is about 2:1.

16. The liposome of claim 14 wherein said molar ratio is about 4:1.

15 17. The liposome of claim 15 wherein said liposome is unilamellar and less than 100 nm.

18. The liposome of claim 17 wherein said hydrogenated soy phosphatidylcholine to GW1843 molar ratio is from about 5:1 to 75:1.

19. The liposome of claim 9 wherein said molar ratio is about 2:1.

20. The liposome of claim 10 wherein said molar ratio is about 2:1.

20 21. The liposome of claim 11 wherein said molar ratio is about 2:1.

22. The liposome of claim 17 wherein said hydrogenated soy phosphatidylcholine to GW1843 molar ratio is from about 8:1 to 20:1.

23. A liposome comprising a benzoquinazoline thymidylate synthase inhibitor (BTSD) encapsulated in a liposome, wherein said liposome is

comprised of hydrogenated soy phosphatidylcholine (HSPC) and cholesterol and wherein HSPC:cholesterol are in a molar ratio of about 2:1, and wherein the HSPC:BTSL molar ratio is from 8:1 to 20:1, and wherein said liposome is unilamellar having a size of less than 100 nm.

5                    24.    The liposome of claim 23 wherein said BTSL is GW1843.

                    25.    The composition of claim 1 produced by the process comprising:

                    a)    forming a lipid film or powder comprised of phosphatidylcholine and cholesterol;

                    b)    hydrating said lipid film or powder with an aqueous solution

10                   containing a benzoquinazoline thymidylate synthase inhibitor (BTSL);

                    c)    applying energy whereby liposomes that are unilamellar and less than 100 nm are obtained;

                    d)    cross-filtering against an aqueous solution to remove unencapsulated BTSL, whereby liposomes containing a BTSL are obtained.

15                   26.    The composition of claim 25 wherein said phosphatidylcholine is selected from the group consisting of distearoylphosphatidylcholine, hydrogenated soy phosphatidylcholine, soy phosphatidylcholine, egg phosphatidylcholine, hydrogenated egg phosphatidylcholine, dipalmitoylphosphatidylcholine, dioleoylphosphatidylcholine,

20                   dielaidoylphosphatidylcholine, and dimyristoylphosphatidylcholine.

                    27.    The composition of claim 26 wherein said phosphatidylcholine is hydrogenated soy phosphatidylcholine.

                    28.    The composition of claim 26 wherein said phosphatidylcholine is soy phosphatidylcholine.

29. The composition of claim 26 wherein said phosphatidylcholine is dioleoylphosphatidylcholine.

30. The composition of claim 26 wherein said phosphatidylcholine is dielaidoylphosphatidylcholine.

5 31. The composition of claim 26 wherein said liposome further comprises phosphatidylglycerol.

32. The composition of claim 25 wherein said energy is applied by a homogenizer.

33. The composition of claim 27 wherein said BTSI is GW1843.

10 34. The composition of claim 28 wherein said BTSI is GW1843.

35. The composition of claim 29 wherein said BTSI is GW1843.

36. The composition of claim 30 wherein said BTSI is GW1843.

37. The composition of claim 31 wherein said BTSI is GW1843.

15 38. The composition of claim 27 wherein the hydrogenated soy phosphatidylcholine to cholesterol molar ratio is from about 5:1 to 2:1.5.

39. The composition of claim 38 wherein said molar ratio is about 2:1.

40. The composition of claim 38 wherein said molar ratio is about 4:1.

20 41. The composition of claim 39 wherein said liposome is unilamellar and less than 100 nm.

42. The composition of claim 41 wherein said hydrogenated soy phosphatidylcholine to GW1843 molar ratio is from about 5:1 to 75:1.

43. The composition of claim 42 wherein said hydrogenated soy phosphatidylcholine to GW1843 molar ratio is from about 8:1 to 20:1.

44. The composition of claim 25 wherein said BTSI is GW1843 and wherein said phosphatidylcholine is hydrogenated soy phosphatidylcholine (HSPC), and wherein said HSPC:cholesterol are in a molar ratio of about 2:1, and wherein the HSPC:BTSI molar ratio is from 8:1 to 20:1.

45. A process for making liposomes comprising a benzoquinazoline thymidylate synthase inhibitor (BTSI), said method comprising:

- a) forming a lipid film or powder comprised of phosphatidylcholine and cholesterol;
- b) hydrating said lipid film or powder with an aqueous solution containing BTSI;
- c) applying energy whereby liposomes that are unilamellar and less than 100 nm are obtained;
- d) cross-filtering against an aqueous solution to remove unencapsulated BTSI, whereby liposomes containing BTSI are obtained.

46. The method of claim 45 wherein said phosphatidylcholine is selected from the group consisting of distearoylphosphatidylcholine, hydrogenated soy phosphatidylcholine, soy phosphatidylcholine, egg phosphatidylcholine, hydrogenated egg phosphatidylcholine, dipalmitoylphosphatidylcholine, dioleoylphosphatidylcholine, dielaidoylphosphatidylcholine, and dimyristoylphosphatidylcholine.

47. The method of claim 46 wherein said phosphatidylcholine is hydrogenated soy phosphatidylcholine.

48. The method of claim 46 wherein said phosphatidylcholine is soy phosphatidylcholine.

49. The method of claim 46 wherein said phosphatidylcholine is dioleoylphosphatidylcholine.

5 50. The method of claim 46 wherein said phosphatidylcholine is dielaidoylphosphatidylcholine.

51. The method of claim 46 wherein said liposome further comprises phosphatidylglycerol.

10 52. The method of claim 45 wherein said energy is applied by a homogenizer.

53. The method of claim 47 wherein said BTSI is GW1843.

54. The method of claim 48 wherein said BTSI is GW1843.

55. The method of claim 49 wherein said BTSI is GW1843.

56. The method of claim 50 wherein said BTSI is GW1843.

15 57. The method of claim 51 wherein said BTSI is GW1843.

58. The method of claim 47 wherein the hydrogenated soy phosphatidylcholine to cholesterol molar ratio is from about 5:1 to 2:1.5.

59. The method of claim 58 wherein said molar ratio is about 2:1.

60. The method of claim 58 wherein said molar ratio is about 4:1.

20 61. The method of claim 59 wherein said liposome is unilamellar and less than 100 nm.

62. The method of claim 61 wherein said hydrogenated soy phosphatidylcholine to GW1843 molar ratio is from about 5:1 to 75:1.

63. The method of claim 62 wherein said hydrogenated soy phosphatidylcholine to GW1843 molar ratio is from about 8:1 to 20:1.

64. The method of claim 45 wherein said BTSI is GW1843 and wherein said phosphatidylcholine is hydrogenated soy phosphatidylcholine (HSPC), and wherein said HSPC:cholesterol are in a molar ratio of about 2:1, and wherein the HSPC:BTSI molar ratio is from 8:1 to 20:1.

65. A method of inhibiting the growth of a tumor comprising the administration of a therapeutic or effective amount of the composition of claim 1 to a tumor.

66. The method of claim 65 wherein said tumor is drug resistant or drug sensitive.

67. The method of claim 65 wherein said tumor is from a cancer selected from the group consisting of ovarian, lung, colorectal, breast, head and neck, prostate, uteran, glioblastoma, and sarcoma.

68. The method of claim 67 wherein said phosphatidylcholine is selected from the group consisting of distearoylphosphatidylcholine, hydrogenated soy phosphatidylcholine, soy phosphatidylcholine, egg phosphatidylcholine, hydrogenated egg phosphatidylcholine, dipalmitoylphosphatidylcholine, dioleoylphosphatidylcholine, dielaidoylphosphatidylcholine, and dimyristoylphosphatidylcholine.

69. The method of claim 68 wherein said phosphatidylcholine is hydrogenated soy phosphatidylcholine.

70. The method of claim 68 wherein said phosphatidylcholine is soy phosphatidylcholine.

71. The method of claim 68 wherein said phosphatidylcholine is dioleoylphosphatidylcholine.

72. The method of claim 68 wherein said phosphatidylcholine is dielaidoylphosphatidylcholine.

5 73. The method of claim 68 wherein said liposome further comprises phosphatidylglycerol.

74. The method of claim 69 wherein said benzoquinazoline thymidylate synthase inhibitor is GW1843.

10 75. The method of claim 70 wherein said benzoquinazoline thymidylate synthase inhibitor is GW1843.

76. The method of claim 71 wherein said benzoquinazoline thymidylate synthase inhibitor is GW1843.

77. The method of claim 72 wherein said benzoquinazoline thymidylate synthase inhibitor is GW1843.

15 78. The method of claim 73 wherein said benzoquinazoline thymidylate synthase inhibitor is GW1843.

79. The method of claim 78 wherein said hydrogenated soy phosphatidylcholine, cholesterol and phosphatidylglycerol are in a molar ratio of about 2:1:0.1.

20 80. The method of claim 74 wherein the hydrogenated soy phosphatidylcholine to cholesterol molar ratio is from about 5:1 to 2:1.5.

81. The method of claim 80 wherein said molar ratio is about 2:1.

82. The method of claim 80 wherein said molar ratio is about 4:1.



83. The method of claim 81 wherein said liposome is unilamellar and less than 100 nm.

84. The method of claim 83 wherein said hydrogenated soy phosphatidylcholine to GW1843 molar ratio is from about 5:1 to 75:1.

5 85. The method of claim 75 wherein said molar ratio is about 2:1.

86. The method of claim 76 wherein said molar ratio is about 2:1.

87. The method of claim 77 wherein said molar ratio is about 2:1.

88. The method of claim 83 wherein said hydrogenated soy phosphatidylcholine to GW1843 molar ratio is from about 8:1 to 20:1.

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